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NUTRITION HIGHLIGHTS — 1951

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NUTRITION HIGHLIGHTS — 1951

By RUTH WOODS

Viewing the progress of nutrition research over the past year, one is left with a strangely paradoxical impression. For, although there have been more discoveries made than perhaps ever before, the nutritionist has become less firmly convinced about many fundamental concepts than ever before. Disquieting as this latter observation may seem at first glance, it must, nevertheless, be regarded as highly encouraging. The doubts and questions and insecurities raised by current research are a healthy sign—a sign of true progress into obscure and labyrinthine pathways which, when finally negotiated, lead ultimately to the goal of comprehension.

In the early days of nutrition the boundaries of our knowledge and research were smaller and simpler to define. The quest was for information as to what components of man's diet were vital to life and health and, in a relatively crude sense, why. From this quest we learned that life can not exist without protein, that fats and carbohydrates provide energy, that infinitesmal traces of accessory substances were needed to prevent the newly recognized deficiency diseases. This was the status of nutrition science not much more than twenty-five years ago.

In the years that followed, these simple but epochal discoveries were enlarged upon and broadened. Painstaking inquiries added numerous new vitamin and mineral factors to the rudimentary "ABC's" of early nutrition studies; the revelation came that proteins meant more than just a source of nitrogen — that amazing qualitative differences existed among proteins — and from this was born the new field of amino acid chemistry and nutrition.

In the last decade, the chemical identification and synthesis of nearly all the vitamins served to remove a great deal of the mystery enshrouding these materials. Concomitant studies in enzyme chemistry linked the vitamins to these versatile catalysts and provided a rational approach to the problem of how vitamins function. Knowledge had begun to replace mystery and obscurity; the principles of nutrition were becoming clear-cut and definable. Nutrition research could be translated into clinical practice; dietary goals and standards could be elaborated; the nutritionist "knew where he was going."

Just as the nutrition picture appeared to be emerging in clear-cut and definite form, however, an imperceptible change began to take place. Having satisfied their curiosity to a considerable extent as to the "what" and "why." of nutrition, scientists began to turn to the intriguing problem of "how". *How* do the now-recognized dietary elements react inside the body to achieve

their observed functions? How do vitamin-enzyme complexes work; how do fat and carbohydrate serve as sources of energy; how does the intake of one nutrient affect the metabolism of a dozen others? In other words, what goes on in the intricate intermediary metabolism of food components?

With the availability of stable and radioactive isotopes and of methods for incorporating these into increasing varieties of biological materials, a potent new tool was made available for probing the intricacies of intermediary metabolism. Out of these studies came the concept of the dynamic equilibrium among body constituents and between these and dietary constituents. The merging of the metabolic pathways of carbohydrate, fat and protein has made it clear that problems concerning the metabolism of any one of these can no longer be considered independently of problems involving the other two. Similarly, the delicately balanced interactions among vitamins, enzymes and hormones have shown that it is not possible to interpret the role of any one of these independently of the action of the others.

Because of this extremely intimate interplay among materials in the biochemical processes of metabolism, new insight into the meaning of nutrition and into an understanding of its relation to health and disease has been made possible. But because of this greater insight, the limitations of present knowledge appear greater than ever. We have become aware, for example, of the fact that such matters as dietary standards and requirements may have to be re-evaluated in many cases depending on numerous other factors. Other studies have shown that rapid, early growth—once regarded as a criterion of excellent development and superior nutrition — may under some circumstances actually be undesirable and lead to overweight and increased incidence of degenerative disease in maturity. In still other studies, doubts—as yet unresolved—have been raised as to whether nutritionally optimal diets are desirable under specialized conditions of abnormal metabolism.

It is apparent that the next few years may be expected to clear up many of these newer problems in nutrition and biochemistry. When the answers to the intriguing questions posed by today's research are found, it is possible that in the "newest knowledge of nutrition" will be provided a means whereby modern degenerative diseases and derangements of metabolism—atherosclerosis, hypertension and other cardiovascular diseases, diabetes, liver disease, kidney disease, rheumatoid diseases, neoplastic disease—may at last be brought under control.

The present Review will describe a limited number of findings made in nutrition and allied fields during 1951. While by no means a complete survey of all the outstanding work done during this busy year, these items con-

stitute a representative list which is likely, in the opinion of the editor, to be of especial interest to the readers of this publication.

Atherosclerosis:

Atherosclerosis, "the nub of cardiovascular disease," and a major cause of death today, was investigated from many new approaches. The concept that this disease is not an inevitable reflection of the aging process but rather a manifestation of abnormal body metabolism has made possible an entirely new method of attack from the research point of view. The role of cholesterol as the etiologic agent and of the phospholipids and certain vitamins as controlling factors in preventing abnormal cholesterol deposition in the arteries has been further studied. The significance of blood lipoprotein fractions of the Sf_{10-20} group, first postulated in 1950 to be closely correlated with the development of atherosclerosis*, was further investigated during 1951 in studies with the ultracentrifuge at the University of California. Although other investigators have questioned the validity of this work upon analysis of the statistical data presented, the California group believes that their most recent studies tend to amplify and corroborate the original premises. Another new development reported by this group is that the anti-coagulant, heparin, is apparently effective in reversing the atheromatic process. The mechanism of action is as yet unexplained. It is intriguing to speculate, however, upon the following: (1) that dissolution of cholesterol deposits by heparin may be similar to reversal of the clotting process, i.e., dissolution of a clot; (2) the relation, if any, of vitamin K, the blood-clotting vitamin whose action is antagonized by heparin to the picture of atherosclerosis.

The significance of lipoproteins in the picture of atherosclerosis was further emphasized in studies at Cornell during 1951. Using the electrophoretic methods and nomenclature of blood fractionation devised by investigators at Harvard, concentrations of the various proteins, of cholesterol and of phospholipids were determined in both normal and atherosclerotic individuals. The arbitary finding of this study at Cornell is that there appears to be both a relative and absolute reduction in the so-called alpha-lipoprotein fraction of blood during atherosclerosis and a concomitant increase, both relative and absolute, in the beta-lipoprotein fraction. It is possible that the beta-lipoprotein group of blood components and the Sf_{10-20} group of lipoproteins may be related, but this has not yet been established.

From a dietary point of view work has continued on the significance of dietary cholesterol and fat as possible precursors of increased cholesterol in

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**cf. Borden's Review of Nutrition Research,* "Cholesterol" October, 1950, and *Borden's Review of Nutrition Research,* "Nutrition Highlights — 1950," January, 1951.

the blood. The California group has shown that a very low-fat, low-cholesterol diet will reduce the level of Sf_{10-20} components in the blood, but further work is needed to establish the clinical significance of this.

Studies in intermediary metabolism have made it clear that cholesterol is synthesized in the body from simple two-carbon compounds such as acetate and that this synthesis is independent of the dietary supply of cholesterol. Acetate can arise from a number of metabolic processes in the metabolism of fats, carbohydrates and proteins. In turn, acetate is utilized not only in the biological synthesis of cholesterol but in the biological resynthesis of many of these components. This has led to the opinion that restriction of calorie intake, may be of more significance in controlling atherosclerosis than restriction of dietary cholesterol *per se,* in that the acetate available for cholesterol synthesis will be minimized. As C. G. King has pointed out:

> "The cholesterol contained in protective foods such as meat, eggs and milk apparently is of far less importance than the quantity formed from surplus fats and sugars within the body. A really basic means of preventing or retarding excessive deposition of cholesterol in tissues such as the arteries, therefore, is to avoid overeating."

Amino Acids:

Studies during 1951 have confirmed preliminary reports as to the indispensable need for eight amino acids in the diet to maintain nitrogen balance in adult man. Other studies have extended original findings on the conversion of the amino acid, tryptophan, to the vitamin, niacin, and have indicated, further, that the reverse process—synthesis of a protein fragment from a vitamin—may actually be possible in certain bacteria.

The origin of the biologically important milk protein, casein, has long puzzled investigators. The component amino acids have been believed by some to be supplied from the blood stream; others have suggested that these are synthesized within the mammary gland. Investigations with isotopically labeled protein fragments have resolved this puzzle by demonstrating actual synthesis of amino acids in the mammary gland to supplement the supply provided by the blood.

Continuing studies on combined amino acids in the form of simple peptides reaffirm earlier reports that some peptides may be more effectively utilized for nutritional purposes than simple amino acids.

Amino Acid-Vitamin-Hormone Interrelations: The direct relation of amino acids to vitamins and to hormones has been indicated in several significant studies during 1951. The microbiologically active combined form of

biotin, i.e. biocytin, was discovered to be a compound containing biotin linked to the amino acid, lysine. Biocytin is identified by the formula, ε-N-biotinyl-L-lysine.

Studies during 1951 on two powerful hormones of the posterior pituitary —oxytocin and vasopressin—have revealed that these are polypeptides each containing eight amino acids; the former composed of leucine, isoleucine, tyrosine, proline, glycine, cystine and glutamic and aspartic acids, while the latter contains arginine and phenylalanine in place of leucine and isoleucine.

New work has been reported on the defective metabolism of the amino acids, tyrosine and phenylalanine, in premature infants on high-protein diets deficient in ascorbic acid*. The long-recognized interrelationship between ascorbic acid and the adrenal gland has stimulated a new approach to the study of this metabolic defect. Studies were made on the ability of the adrenal-stimulating hormone, ACTH, as well as of adrenal hormones themselves (cortisone, desoxycorticosterone, compound "L", progesterone, etc.) to replace ascorbic acid in correcting the defective metabolism of the aromatic amino acids. ACTH consistently abolished the defect; cortisone was less effective; the other hormones tested were ineffective. Although the mechanism of action is not yet known, it is suggested that either ACTH stimulates the premature adrenal to manufacture extremely large amounts of cortisone, or that it increases the secretion of one or more of the other adrenocortical hormones which may then act alone or together to correct the defect. Ascorbic acid was more effective than even ACTH.

The relation of ascorbic acid to tyrosine metabolism has been explained from at least one point of view by other investigators who have demonstrated that this vitamin serves as a coenzyme in the enzymatic oxidation of tyrosine following its preliminary deamination. What the relationship may be between this mechanism and the effect of ACTH on tyrosine metabolism in ascorbic acid deficiency still remains obscure. One thing is known, namely that ACTH does not act by mobilizing stored vitamin C as evidenced by failure to find increased levels of the vitamin in the plasma or urine.

Newer Vitamins:

Citrovorum Factor: During 1951 studies with the citrovorum factor (CF) have continued from both experimental and clinical points of view. Synthesis of a compound very similar to, but probably not identical with CF, was announced. The synthetic compound is 5-formyl-5,6,7,8-tetrahydropte-

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*cf. *Borden's Review of Nutrition Research*, "Dietary Interrelationships: Vitamin C and the Metabolism of Aromatic Amino Acids," September, 1949.

roylglutamic acid, obviously a derivative of folic acid (pteroylglutamic) as suggested by earlier experiments. CF is apparently a metabolic product of folic acid. It seems to be involved in the requirement for single carbon fragments which are essential for the subsequent synthesis of purines and, possibly, for the synthesis of the methyl groups of choline, methionine and thymine under certain conditions.

L. Bulgaricus Factor: The *Lactobacillus bulgaricus* factors described a few years ago have been further studied and at least one member of this group identified as a derivative of pantothenic acid (i.e. N-(pantothenyl)-β-amino-ethanethiol). This material is also believed to be part of the coenzyme A molecule in conjunction with a derivative of ATP.

α Lipoic Acid: A new factor from liver has been isolated in crystalline form. It is believed to be a new B vitamin because of its biological behavior. Unlike other B vitamins, however, it is highly fat-soluble. The new factor appears to be involved in the oxidative decarboxylation of pyruvate to yield acetate. Because it is fat-soluble, acidic and an indirect precursor of fatty acids via acetate, the vitamin — one of a group of related materials — has been given the name alpha lipoic acid. Alpha lipoic acid is highly active as a growth stimulant in replacing acetate in the nutrition of *S. lactis*. Studies are in progress to determine the chemical nature and biological activity of this substance. One is led to speculate on the possible significance of this new factor in favoring those metabolic pathways which give rise to acetate and, in so doing, to increase the acetate available not only for fatty acid synthesis, but for cholesterol synthesis as well. Whether a metabolic antagonist of alpha-lipoic acid may be found, and whether this might decrease excess acetate formation conceivably to minimize cholesterol biosynthesis and so, ultimately, retard the development of atheromatic lesions are other thoughts which present themselves.

Other Vitamins: Studies during 1951 have further elaborated the biological behavior of vitamin Bt—first described in 1948—and have established its identity as carnitine. This vitamin, essential for growth and survival of the mealworm (*Tenebrio molitor*) has been isolated from yeast and liver extracts. Eggs and vegetable materials are poor sources of this factor, while powdered milk and powdered whey appear to be considerably more potent than even liver and yeast.

Lyxoflavin is another new vitamin reported during 1951 as a nutritional essential for the rat and for certain microorganisms. It is closely related to riboflavin, differing only in the substitution of the isomeric sugar, lyxose, for ribose.

Phospholipids:

The biological role of phospholipids in fat metabolism, as lipotropic factors themselves (lecithin) or as sources of such agents as choline and inositol has received renewed attention during 1951. Much of the work has centered on the role and possible significance of these compounds in atherosclerosis. General findings of these studies indicate that the importance of the phospholipids may be in maintaining a sufficiently high level of such materials in the plasma in relation to the amount of cholesterol present. The phospholipids, because of their hydrotropic nature, apparently stabilize cholesterol in colloidal dispersion in the plasma. They thereby minimize the tendency of cholesterol to precipitate, and to form deposits leading to atherosclerosis. These findings offer a possible explanation for the numerous contradictory findings concerning the significance of high cholesterol or high lipid levels in the blood. In other words, it may not be an elevated blood cholesterol level *per se* which leads to atherosclerosis but rather the cholesterol: phospholipid ratio which determines whether or not cholesterol—whether quantitatively high or low—will be precipitated out of the plasma. An increase in phospholipids, therefore, may tend to stabilize excessive blood cholesterol and thus prevent atherosclerosis whereas, in the absence of sufficient plasma phospholipid, even a relatively low blood level of cholesterol may prove hazardous since it may tend to be precipitated and deposited in the arteries. These studies suggest, therefore, that dietary consideration should be given not only to fat and cholesterol intakes and to excessive calories (as sources of acetate for cholesterol biosynthesis), but to adequacy of dietary sources of phospholipids and of phospholipid precursors. In addition to this role, the phospholipids such as lecithin appear to be of significance in correcting problems related to disturbed lipid metabolism. These concern such diverse manifestations as liver and kidney dys-functions, skin disorders, faulty fat absorption and others.

Public Health:

Enrichment: Results of a decade of bread enrichment in the United States were noted during 1951. Nutrition surveys and experimental studies have emphasized the appreciable contributions made to public health as a result of this program. This subject will be amplified in a forthcoming issue of this publication. Nutrition surveys recently completed in the Philippines have correlated diet studies, public health statistics and clinical findings obtained following the introduction and operation of the rice enrichment program with data from similar sources prior to the establishment of this public health measure. Decreased mortality and morbidity rates and improved gen-

eral nutritional status among the populace in the experimental area attested to the outstanding contributions of this large-scale public health experiment. This story will be discussed more fully in the February 1952 issue of *Borden's Review of Nutrition Research.*

Fluoridation: Continuation and expansion of the program for fluoridation of public water supplies has been reflected in appreciable decreases in the incidence of dental caries among children consuming this water*. Long term studies have confirmed the value of carefully controlled fluoride addition and have re-emphasized the absence of any deleterious effects on health resulting from such measures.

Obesity: The growing awareness of obesity and even moderate overweight as major hazards to public health and mortality reached a peak during 1951. Recognized as the "No. 1 problem in preventive medicine today," and as a leading cause of increased mortality and heightened incidence of degenerative diseases, the problem of obesity has stimulated many efforts to combat this widespread public health hazard. New statistical and experimental findings were reported by the Metropolitan Life Insurance Company and a symposium on problems of overweight constituted an important feature of the 1951 convention of the American Medical Association.

Attempts to define and quantitatively estimate overweight more clearly have been made and norms for the evaluation of fatness-leanness have been developed.

The apparent superiority of low-calorie reducing diets composed chiefly of protein and fat in contrast to the usual protein-carbohydrate reducing diets has been reported. The efficacy of these diets has been attributed to the fact that no change in basal metabolic rate occurs on the low calorie, fat-protein reducing diet. When the same number of calories is provided by a carbohydrate-protein diet, however, there appears to be a compensatory drop in the B.M.R. which, by apparently allowing the body to adapt to the lowered calorie intake, prevents any significant weight loss.

Undernutrition: The occurrence of underweight constitutes a problem of equally widespread proportion to that of obesity, although the hazards involved are of a lesser order of magnitude. In many instances attempts at gaining weight have proved to be almost as difficult as the efforts of obese persons to lose weight. The problem of calorie supplementation was originally studied in connection with parenteral nutrition. A stable fat emulsion was devised in order to supply sufficient calories for weight maintenance,

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**cf. Borden's Review of Nutrition Research,* "Fluorine and Dental Health," December, 1942 and "The Role of Fluorine in the Diet," March, 1948.

since dextrose and amino acids are inadequate in this respect. Arising from this development, a fat emulsion was devised for oral use. This product consists essentially of an emulsion of 40% oil and 10% dextrose in water. This product supplies a means of supplementing the diet with a large number of calories in concentrated form and has been reported to be effective in increasing weight.

Animal Nutrition:

Antibiotics: The big story in animal nutrition continued to be the use of antibiotics as supplements to feeds. Numerous studies have been reported on the value of these materials in promoting growth and decreasing mortality rates on standard rations both alone and in conjunction with vitamin B_{12} and the animal protein factor complex. The mechanisms whereby these results are obtained are not yet fully known, although it is apparent that the antibiotics exert their influence by altering bacterial conditions in the intestine. Possible ways in which this occurs include: (a) inhibition of certain bacteria which tend to destroy, or utilize for their own needs essential nutrients supplied by the food; (b) stimulation of the growth of favorable bacterial types over other types resulting in a greater synthesis of useful nutrients by the former; (c) less injury to the animals by small amounts of toxic products normally formed in the intestinal tract.

Full evaluation of the use of antibiotics in feeds, however, must await long-term study to determine their long-range effects on the health of both livestock and of the human consumer. The eventual use of antibiotics directly in human feeding is another potentiality, but this, too, will necessarily await further studies on the mechanisms involved and the possible risks or complications, if any, which may ensue.

Other Nutrients: Studies during 1951 indicate that dried whey contains unidentified nutrients essential for maximum chick growth. Improvements in weight gain on an all vegetable protein diet were obtained when the ration was supplemented with 3–5% of dried whey. This improvement was noted even when the feed was already supplemented with an APF concentrate and antibiotics.

In recent years urea has been used successfully in ruminant feeds to replace or substitute for part of the dietary protein requirement. This is possible because bacterial action in the rumen leads to the synthesis of amino acids from urea nitrogen. Because urea contains no sulfur, however, it is impossible for the ruminant to synthesize the sulfur-containing amino acids, methionine and cystine. Radio-isotope experiments conducted last year, how-

ever, demonstrated that these sulfur amino acids can indeed be synthesized in the rumen if inorganic sulfates are included in the diet. Furthermore, feeding studies showed that lambs can grow on purified diets containing urea as the only source of nitrogen if this is supplemented with inorganic sulfates. The possible economic significance of this cannot be estimated until further large-scale animal feeding studies are completed.

Vitamin B_{12} and Folic Acid:

Clinical and experimental studies continued during 1951 on the use of this group of vitamins in combating various types of anemias. The intricate interrelations among vitamin B_{12}, folic acid, citrovorum factor, vitamin C, lipotropic agents, methylating agents and certain amino acids* have been further explored. A newly observed interrelation is that vitamin B_{12} and pantothenic acid, under certain conditions, appear to exert a mutually sparing action on each other.

A somewhat surprising development has been the observation of a significant relationship between folic acid and the central nervous system. This relationship is unexpected in view of the fact that while both folic acid and B_{12} are effective in improving the blood picture in pernicious anemia, the neurological complications respond only to vitamin B_{12}. That folic acid does influence the nervous system in other ways, however, has been shown by studies which reveal that administration of folic acid to pregnant rats protects against the development of hydrocephalus in the offspring. Severe deficiencies of folic acid in the diet of pregnant rats such as are induced by folic acid inhibitors lead to congenital malformations of various other organs, or even complete resorption of the fetus.

A further relationship of folic acid to the brain has been noted in that marginal dietary deficiency of this vitamin in pregnant rats apparently exerts a deleterious effect upon mental performance in the offspring as evidenced by decreased capacities for maze learning. This brings to mind again the reputed effect of glutamic acid in increasing mental ability both in rats and in human subjects with certain types of mental deficiency. Although much criticism and doubt has been cast on this work, it is significant that glutamic acid is an integral part of the folic acid molecule. The excretion of excessive quantities of glutamic acid in the urine during folic acid deficiency in the rat, reported early in 1951, adds another fragment to this as yet uncompleted picture.

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*For a summary of these interrelationships, see *Borden's Review of Nutrition Research*, "Nutrition Highlights — 1950," January, 1951.

Problems in Human Nutrition:

Nutritional Interrelationships: The increasingly apparent interdependence of the various vitamins, of the various amino acids, of the vitamins and amino acids, of both of these with the hormones, and of all of these with the minerals and the general composition of the diet as a whole make it exceedingly difficult to estimate, with any degree of precision, the quantitative dietary requirements for each of these factors. Current researches in intermediary metabolism revealing that many of the gross dietary components such as fats and sugar have certain common metabolic pathways further complicate this problem. Thus, the planning of nutritionally adequate diets must take into account the fact that it is no longer meaningful to consider the role or requirement of an individual ingredient — each nutrient must be related, both qualitatively and quantitatively, to the composition of the over-all diet. The effect of balances, partial substitutions and other interacting mechanisms must be evaluated and the broad concept must be developed that there are more ways than one to achieve dietary adequacy. This concept is of extreme importance in practical nutrition programs dealing with the planning of diets for population groups in various geographical areas where agricultural, economic and social problems may preclude the consumption of diets patterned after our own particular standards.

Individual Metabolic Patterns: During 1951, an extremely thought-provoking report appeared summarizing studies which place great emphasis on the variations in individual patterns of body function in the use of food. Genetic differences in enzyme patterns which control biochemical reactions in the body are believed to form the basis for the striking variations found among "normal" individuals. This so-called genetotrophic approach offers an explanation for the development of nutritional deficiencies of some persons on apparently adequate diets. The genetotrophic concept of disease — including alcoholism, mental derangement, degenerative and metabolic diseases, etc. — similarly relates predisposition to certain diseases to individual variations in metabolism and in nutritional requirements. These studies have emphasized the need for generous margins of safety in food and nutrient recommendations to protect those individuals whose requirements for one or more essentials may be outside the so-called average requirements.

Optimum Diets: Aside from the intricacies imposed by the interrelations and balances among the various nutrients, and the obvious variations in requirements among "normal" individuals, the practical nutritionist is faced with the problem of deciding what are general optimum levels of nutrition toward which to aim. Here again, the existing evidence is far from clear

or final. There have been excellent animal studies to indicate that hyperalimentation with certain nutrients — notably riboflavin, vitamin A and calcium — significantly increases the normal life span, lengthens the "prime of life" period and produces superior young. On the other hand, there have been equally excellent studies to indicate that restriction of the diet, particularly with respect to calories, to the point where growth rate is limited, leads to increased longevity and an appreciable decrease in the incidence of many degenerative diseases. Other studies have presented provocative findings which indicate that rapid growth and development during childhood* may not be as desirable a goal as is generally believed. Under such circumstances, too, there may develop a predisposition to obesity and degenerative disease during subsequent maturity. Again, there have been recent animal studies indicating that *brief periods* of nutritional inadequacy during early life—even though subsequently corrected so that apparently normal progress is made—may explode into serious repercussions in later maturity in the form of various degenerative diseases. This is the so-called "time bomb" aspect of nutrition which has begun only recently to be appreciated.

Confusing as these facts may be at present, there is still considerable evidence that (1) the recommended daily allowances of the Food and Nutrition Board and (2) the "basic seven food groups" — are reliable general guides to the planning of adequate diets. One might conclude that moderation in calories, adequate provision of all the known nutritional essentials, without either undue emphasis on or extreme restriction of any one nutrient is the best nutrition goal in the light of present knowledge.

*Representing not only high calorie levels, but high levels of protein and other nutrients as well.